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## Sex-sensitive cognitive performance in untreated patients with early onset gender identity disorder

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### Abstract

**Background.** We explored whether the cognitive performance of gender identity disorder patients (GID) was comparable to that of their biological sex or skewed towards that of their gender identity.

**Method.** We tested four potentially sex-sensitive cognitive factors (rotation, visualization, perception, and verbalization) as well as two neutral factors (logic and arithmetic) in GID patients from Norway (GID-N,  $n=33$ ) or the USA (GID-US,  $n=19$ ) and in a control group (C,  $n=29$ ). The testing was undertaken prior to cross sex hormone treatment. Four-way ANOVA was applied in the final analysis of the cognitive performance and its dependency on different predictors (age, biological sex, education, group).

**Results.** In both GID groups as well as in the control group (C) males excelled in visualization and rotation, also when controlling for potential confounders (biological sex, group, age and education). No female advantage was detected. Furthermore, no interaction between biological sex and group assignment was revealed in the samples.

**Conclusion.** In this study the cognitive pattern of GID patients is consistent with that of their biological sex and not that of their gender identity.

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**Keywords:** Cognitive ability; Neuropsychological testing; Sex sensitive differences; Cognitive pattern; Gender identity

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## 1. Introduction

Gender identity disorder of adults (GID, DSM IV 302.85) (APA, 1994) is characterized by a discrepancy between biological sex and gender identification, expressed as a feeling of being born with the wrong sex. Recognized since antiquity (Foucault, 1976), the etiology of GID remains unknown. Theories range from psychodynamic conflicts and defects of psychosexual development to biologically oriented hypotheses (Lothstein, 1982; LeVay and Hamer, 1994; Zhou et al., 1995; Kruijver et al., 2000). Regardless of etiological controversy, evidence has been presented that the sex-sensitive cognitive performance of GID patients is skewed away from that of their biological sex towards that of their perceived gender. However, only one study has investigated untreated early onset patients (Cohen-Kettenis et al., 1998). The authors observed less pronounced sex differences in GID patients compared to normal controls and argued that less functional brain lateralization in male GID patients compared to control males might reflect a more feminized brain structure. Instead, most studies of cognitive function in GID patients have been limited to examination during cross-sex hormone therapy, and the results suggest that cross-sex hormone treatment might cause cognitive changes in GID patients (van Goozen et al., 1994; Miles et al., 1998; Slabbekoorn et al., 1999).

In healthy men and women sex-sensitive patterns of cognitive performance have been thoroughly described (Linn and Petersen, 1985; Silverman and Phillips, 1993; McKeever, 1995; Voyer et al., 1995; James and Kimura, 1997; Janowsky et al., 1998; Halpern, 2000), although the replication of neuropsychological testing appears to have provoked strong methodological discussions (McKeever, 1995). Furthermore, a unifying causal hypothesis has not been presented. It has been proposed that sex hormones influence embryonic brain development (Dohler et al., 1984; Geschwind and Galaburda, 1985; Williams and Meck, 1990; Swaab et al., 1995; McEwen, 1997) or modulate cognitive performance in adult life (Christiansen and Knusmann, 1987; Hampson and Kimura, 1988; Gouchie and Kimura, 1990; Sherwin, 1994). On the other hand, neuropsychological sex-differences may be influenced not only by a certain cognitive ability, but also by an interplay with complex psychosocial factors (Breedlove, 1997). The strongest evidence for prenatally influenced cognitive function is observed in endocrine disorders such as congenital adrenal hyperplasia (CAH) in which adolescent females display a cognitive performance skewed towards that of healthy males despite postnatal female hormone treatment (Resnick et al., 1986; Hampson et al., 1998; Kelso et al., 1999). On the other hand, GID patients show endocrinological parameters comparable to their biological sex and until now, no known genetic defect has been found.

The aim of the present study was to evaluate the cognitive function of young, somatically healthy early onset GID patients before hormone treatment, testing whether they showed a pattern comparable to their same sex control group or not, while controlling for potential confounders.

## 2. Material and methods

### 2.1. Subjects

This study included 52 somatically healthy early onset GID patients who consecutively sought sex reassignment surgery (SRS) in Norway from 1996 to 1998 [GID-N,  $n=33$ , 21 females, 12 males, mean age (SD)=26.7 (5.9) years] or from the free-standing private Gender Center, Palo Alto, CA in 1997 and 1998 [GID-US,  $n=19$ , 9 females, 10 males, mean age (SD)=35.2 (10.0) years]. All patients were evaluated according to the Harry Benjamin International Gender Dysphoria Association's Standards of Care [1990 and 1998 (Levine et al., 1998)]. Furthermore, in two independent comprehensive evaluations by two senior psychiatrists all patients fulfilled the criteria for GID according to DSM IV and the Swedish selection criteria for SRS (Wålinder et al., 1977). All included GID patients were diagnosed as early onset GID patients, fulfilling criteria A to D in DSM-IV from childhood on. They were either homosexually attracted by males or females ( $n=38$ ), by both ( $n=3$ ) or by neither ( $n=9$ ) at the time point of investigation. Two patients reported homosexual orientation to their acquired gender.

Neuropsychological testing was performed before cross sex hormone treatment started. All participants were chromosomally and endocrinologically screened, and free of medication. Participants with any endocrinological, genetical, neurological or major psychiatric comorbidity were excluded [ $n=3$ , from GID-N (two delusional disorders, one XXY anomaly)].

Furthermore, the control group (C) members were heterosexual Norwegian participants with no lifetime diagnosis of gender identity disorder. They were either high school graduates, military recruits from the armed forces, college students or employees of the University of Oslo [ $n=29$ , 15 females; 14 males, mean age (SD)=24.3 (10.2) years]. They were recruited by advertisement.

The age distribution in an independent sample *t*-test did not differ ( $p=0.8$ , mean difference=0.5 years) between females [ $n=45$ , female mean age (SD)=28.4 ( $\pm 10.3$  years)] and males [ $n=36$ ; 27.9 ( $\pm 9.2$ ) years]. The age distribution was also equal between Control and GID-N groups ( $p=0.5$ , mean difference=1.55 years) but differed between Controls and both GID ( $p=0.04$ , mean difference=−9.1 years) because of the older GID-US group.

The education level of all participants ( $n=81$ ) was scored and categorized as follows: 1=high school graduates ( $n=27$ ); 2=college graduates ( $n=43$ ); 3=higher university degree ( $n=11$ ). Uncorrected one-way ANOVA revealed significant differences between all groups ( $F=71.9$ ,  $p<0.0005$ ). Thus, the lowest education level was found in the GID-N group (78.8% with only high school degree) and the highest level in the GID-US group (52.6% with university degree). There was no difference as to education between females and males.

All participants in this study were right-handed.

The study was approved by the Human Approval Board at Stanford University, Palo Alto, CA. It was also performed according to national legislation and institutional guidelines in Norway. All participants signed an informed consent.

## 2.2. Neuropsychological tests

Six cognitive factors (rotation, visualization, perception, verbalization, logic, arithmetic) were examined by a selection of 11 tests from "Kit of factor-referenced cognitive tests", which is methodologically based on a factor analysis (Ekström et al., 1976). All cognitive factors were represented by two tests, except perception (one test). Each test was administered twice in two different versions.

The tests were selected to represent cognitive factors, which reveal significant sex differences according to earlier studies (van Goozen et al., 1994; Voyer et al., 1995; Cohen-Kettenis et al., 1998). Thus, rotation and visualization were expected to favor males; perception and verbalization to favor females; and logic and arithmetic to be neutral. The mean of all test scores representing one cognitive factor was used for further analyses.

*Rotation* was assessed by means of the card rotation test and the cube comparison test. In the former, the subject picks the one out of eight figures, which represents a mirrored or rotated version of the stimulus figure. Three minutes are available for 10 exercises. In the latter test, a pair of imaged cubes, each with a different orientation, is determined to be identical or not. Three minutes are available for 21 exercises.

*Visualization* was assessed by means of the form board test and the paper folding test. In the former, a figure must be constructed by assembling up to five figures. Eight minutes are available for 24 exercises. In the latter test, a picture illustrates a folded piece of paper with a punched hole. Out of five additional pictures the subject picks the one that represents the identical, but unfolded paper by determining the new position of the hole(s). Three minutes are given for 10 exercises.

*Perception* was assessed by means of the identical pictures test in which 48 figures are evaluated in 1.5 min. Out of five figures the subject picks one that is identical to the stimulus figure.

*Verbalization* was assessed by means of word ending test and the word beginning test. The subject writes as many words as possible with a given pre- or suffix within 3 min.

*Logic* was assessed by means of the nonsense test and the diagramming relationship test. In the former the subject is asked for the logic reasoning of two sentences that leads to the concluding third sentence. Four minutes are available for 15 exercises. In the latter test, "Venn diagram" styled geometric figures representing the relationship between three words. Five different diagrams are presented for each exercise. Four minutes are available for 15 exercises.

*Arithmetic* was assessed by means of the arithmetic aptitude test and the arithmetic operation test. In the former, fifteen minutes are available for 15 calculations. Results are picked from five alternative answers. In the latter test, 15 min are available for 15 calculations in which the subject picks the correct arithmetic operation required for a given result (addition, subtraction etc.).

Each test session started at 0900h and lasted for 3 h with two 15 min breaks after the first and second hour. The order of test presentation was random and administered by one of two trained test assistants, to all participants, including controls.

### 2.3. Statistics

Independent sample *t*-tests were used for simple primary statistics. One-way and four-way ANOVAs were applied to the cognitive abilities and their dependency on different predictors (Altman, 1991). The analyses and the checking of required assumptions were implemented in SPSS 11.0 (SPSS, 2001). The cognitive factors (rotation, visualization, perception, verbalization, logic and arithmetic) served as dependent variables whereas biological sex (female, male), education (graduated from high school, college, university) and group (GID-US, GID-N, C) were predictors. Age was treated as a covariate predictor, because of its continuous distribution. All interactions between predictor variables were tested. Post hoc comparisons were performed. The significance level was set at 0.05 and a confidence interval of 95% was used.

## 3. Results

The analysis of variance (ANOVA) was performed in two steps: One-way ANOVAs was performed with group (C, GID-N, GID-US) as a factor and the various cognitive test results as dependent variables. Finally, age, sex and education were introduced in four-way ANOVAs to check for confounding. Post-hoc comparisons are reported. All neuropsychological test results were normally distributed (data not shown). Table 1 describes mean measures split by born genetic sex and group.

Uncorrected one-way ANOVA between the groups revealed that the control group scored significantly higher than the GID-N group in perception [mean difference (confidence interval)=6.0 (1.5–10.5),  $p=0.005$ ], visualization [2.9 (0.4–5.3), 0.02] and verbalization [2.9 (0.2–5.6), 0.04]. Furthermore, the C group scored significantly higher than the GID-US group in perception [7.6 (2.4–12.8), 0.002], but significantly lower in arithmetic [−2.3 (−3.6 to −1.0), 0.0005] and logic [−1.4 (−2.8 to −0.13), 0.03]. Moreover GID-US patients scored significantly better than GID-N patients in arithmetic [−3.3 (−4.6 to −2.1), 0.0005] and logic [−2.4 (−3.7 to −1.1), 0.0005].

Uncorrected one-way ANOVA with sex as between factor revealed a significant male advantage in rotation [−1.23 (−2.08 to −0.39), 0.05] and in visualization [−2.40 (−4.16 to −0.80), 0.008].

To correct for the potential confounders (age, biological sex, education) on the variable of interest, i.e., group, we performed four-way ANOVAs in the next step of analysis (Table 2).

Only biological sex significantly explained the variation in rotation and visualization results (Table 2; males scored higher than females). The education level correlated positively with scores in logic, arithmetic and verbalization (Table 2). Moreover, age significantly explained variation in perception and verbalization (younger subjects achieved higher scores), as well as arithmetic (older subjects obtained higher scores). Interactions between each of the predictors were not found. In particular, no interaction between biological sex and group assignment (Table 2) was revealed, thus demonstrating that none of the sex differences between males and females varied

Table 1  
Mean test scores by group and sex

Cognitive factor	C (n=29)		GID-N (n=33)		GID-US (n=19)	
	females	males	females	males	females	males
Rotation	3.8 (2.7–4.8) <sup>a</sup>	5.2 (4.5–5.9)	3.6 (2.5–4.7)	4.3 (3.3–5.4)	3.7 (1.9–5.4)	5.2 (4.3–6.1)
Visualization	10.0 (8.2–11.9)	11.4 (9.5–13.4)	7.3 (5.2–9.3)	8.8 (7.0–10.5)	8.4 (5.4–11.4)	12.4 (9.4–15.5)
Perception	41.2 (37.8–44.6)	39.3 (36.7–41.8)	36.1 (32.4–39.8)	31.5 (27.2–34.8)	31.1 (24.4–37.8)	34.1 (28.4–39.7)
Verbalization	15.2 (13.3–17.0)	15.2 (13.3–17.1)	12.6 (10.0–15.2)	11.9 (9.9–13.9)	12.5 (8.9–16.1)	14.1 (11.0–17.3)
Logic	6.5 (5.7–7.3)	6.8 (5.7–7.8)	5.8 (5.0–6.5)	5.7 (4.7–6.6)	7.2 (5.3–9.2)	8.9 (7.3–10.6)
Arithmetic	5.1 (4.7–5.7)	5.3 (4.5–6.1)	4.1 (3.2–4.9)	4.2 (3.4–4.9)	6.9 (4.8–9.1)	7.9 (6.1–9.7)

<sup>a</sup> Mean (confidence interval).

Table 2  
The influence of biological sex, group, education and age on six cognitive factors (four way ANOVAs)

Cognitive factor	Main effects		Interaction			
	Biological sex <i>p</i>	Group <i>p</i>	<i>p</i> contrast: C vs. GID-US	<i>p</i> contrast: GID-N vs. GID-US	Education <i>p</i>	<i>p</i> contrast: Biological sex <i>p</i>
Rotation	<b>0.02<sup>a</sup></b>	<b>0.91</b>	<b>0.47</b>		<b>0.80</b>	<b>1.00</b>
Visualization	<b>0.04<sup>a</sup></b>	<b>0.50</b>	<b>0.16</b>		<b>0.34</b>	<b>0.70</b>
Perception	<b>0.14</b>	<b>0.003<sup>a</sup></b>	<b>0.001<sup>a</sup> 0.159</b>	<b>0.07</b>	<b>0.03<sup>a</sup></b>	<b>0.31</b>
Verbalization	<b>0.90</b>	<b>0.02<sup>a</sup></b>	<b>0.006<sup>a</sup> 0.017<sup>a</sup></b>	<b>0.006<sup>a</sup></b>	<b>0.008<sup>a</sup> 0.428</b>	<b>0.005<sup>a</sup></b>
Logic	<b>0.40</b>	<b>0.89</b>			<b>0.003<sup>a</sup></b>	<b>0.57</b>
Arithmetic	<b>0.50</b>	<b>0.34</b>	<b>0.04<sup>a</sup></b>	<b>0.04<sup>a</sup></b>	<b>0.011<sup>a</sup></b>	<b>0.28</b>
					<b>0.0005<sup>a</sup></b>	
					<b>0.029<sup>a</sup></b>	

<sup>a</sup> Statistically significant differences. (fixed factor: group, biological sex, education; covariate factor: age. Dependent factor: each cognitive factor).

significantly between the groups. Although scores in verbalization and perception differed between C, GID-N and GID-US groups (Tables 1 and 2), the influence of biological sex and the interaction between biological sex and group was indeed similar in all three groups. Thus, the presence of GID had no impact on the cognitive test results of sex-associated factors within each group.

#### 4. Discussion

By performing detailed ANOVAs and controlling for relevant predictors this study reveals that both GID and control males excel in “male” cognitive factors. Our data suggest that both GID patients and controls show the most stable sex difference in rotation as reported in many studies of normal populations (Williams and Meck, 1990; McKeever, 1995; Voyer et al., 1995). In fact, we found that rotation and visualization were significantly influenced only by one predictor namely biological sex (Table 2), whereas none of the other variables significantly influenced these two cognitive factors.

The previously described female advantage in perception and verbalization in healthy controls (Kimura, 1992; James and Kimura, 1997), as well as in male early-onset GID patients in verbalization (Cohen-Kettenis et al., 1998), could not be confirmed in our study. Although there were still group differences in perception and verbalization after introducing four predictors in the analysis, neither the main effect of biological sex nor the interaction of group and biological sex could explain these group differences (Table 2). Several explanations are possible. First, a different pre/suffix distribution in the two languages could be responsible for the group differences in verbalization. Second, verbal fluency and not other verbalization abilities were tested. In verbal memory tests, for example, females with estrogen deficiency do worse when compared to a substituted group (Sherwin, 1994). Nevertheless, the included GID patients had no endocrine abnormalities according their biological sex. Furthermore, it should be noted that the sex specificity of the cognitive ability verbalization has been questioned (Lamielle, 1995; Kramer et al., 1997). Third, a limitation might be that a more difficult test than Ekstrøm's identical pictures test (Ekstrøm et al., 1976), for instance a location exchange test, could have precipitated the expected female advantage for perception. Fourth, a larger GID-US sample could have modified the estimation of perception or a control sample drawn from the US society might have clarified the group differences. Nevertheless, the negative result of the interaction between group and biological sex in all samples and the similar pattern of GID-N and C groups resulted in cognitive ability scores independent of the gender identity for perception.

A strong association between the predictor age and some cognitive factors was observed (Table 2). The decline of verbal ability with increasing age observed in the present study is in agreement with a recent study (Meguro et al., 2000). Furthermore, older subjects scored significantly higher than the younger participants in arithmetic (Table 2). The latter might be interpreted as an effect of changed learning attitudes (less training in hand written calculations).

The expected “neutral” tests (logic, arithmetic) were included to meet the requirements of a follow-up study for methodological reasons (Haraldsen et al., manuscript submitted). We wished to include tests, which should not be associated with biological sex, but instead by other predictors. This study revealed clearly that logic was only associated with the predictor education. Furthermore, more highly educated subjects scored better in arithmetic, verbalization and (of marginal significance) perception scores (Table 2).

A principal limitation could be the sample selection. However, in Norway everyone has access to the same public health care system, and socioeconomic background is less likely to influence sample composition (Statistics, 2002). Nevertheless, group differences were only seen in the variables perception and verbalization as discussed above, and no interaction between biological sex and group for these cognitive factors was found. Furthermore, the older American patients belong to the same diagnostic group, but probably because of a different health care system (private vs. public) the US patients were generally some years older before searching for SRS surgery than the Scandinavian patients. However, this difference was of no disadvantage to our study, but instead provided more variance with regard to age and education and enabled the identification of age (as well as education) as confounders.

To the best of our knowledge, only one previous study has addressed sex-sensitive patterns of cognitive performance in patients with early onset GID before starting cross sex hormone treatment (Cohen-Kettenis et al., 1998), concluding that significant differences between early onset GID patients and controls exist. Our data are partly at variance with that study. Thus, in verbal memory Cohen-Kettenis et al. (1998) observed less prominent sex differences in GID patients than in controls. However, the influence of age and education was not investigated. Although the samples were age matched, such matching may underestimate the influence of the variable. The education level of the samples was not stated. Furthermore, they did not document any difference between male GID patients and male controls with regards to the spatial rotation tests, a finding confirmed in our study.

In conclusion, almost all primary differences between the groups in this study could be explained by carefully analyzing the influence of biological sex, age and education. Thus, our findings do not support the view that GID patients show a cognitive pattern different from healthy controls. First, biological sex predicted similar rotation and visualization test results in all groups despite their different gender identity. Second, none of the cognitive factors revealed a biological sex and group assignment interaction for any of the cognitive factors (Table 2). Instead, we show that GID patients of this sample perform neuropsychologically similar to a control sample.

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